10

20

What is claimed is:



A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to the mammal a therapeuticallyeffective amount of a combination of a cyclooxygenase-2 inhibitor and one or more antineoplastic agents, wherein said antineoplastic agents are selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Coll Pathways CP-461, docetaxel, doxorubicin, etoposide, fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), sulindac sulfone, exemestane,

- 2. The method of Claim 1 wherein the combination is administered in a sequential manner.
- 3. The method of Claim 1 wherein the combination is administered in a substantially simultaneous manner.
- 25 4. The method of Claim 1 wherein the antineoplastic agent is capecitabine.

and eflornithine (DFMO).

- 5. The method of Claim 1 wherein the antineoplastic agent is carboplatin.
- 6. The method of Claim 1 wherein the antineoplastic agent is cisplatin.

-177-

- 7. The method of Claim 1 wherein the antineoplastic agent is Cell Pathways CP-461.
- 8. The method of Claim 1 wherein the antineoplastic agent is docetaxel.
- 5 9. The method of Claim 1 wherein the antineoplastic agent is doxorubicin.
 - 10. The method of Claim 1 wherein the antineoplastic agent is etoposide.
- 11. The method of Claim 1 wherein the 10 antineoplastic agent is fluoxymestrine.
 - 12. The method of Claim 1 wherein the antineoplastic agent is gemcitabine.
 - 13. The method of Claim 1 wherein the antineoplastic agent is goserelin.
- 15 14. The method of Claim 1 wherein the antineoplastic agent is irinotecan.
 - 15. The method of Claim 1 wherein the antineoplastic agent is ketoconazole.
- 16. The method of Claim 1 wherein the 20 antineoplastic agent is letrozol.
 - 17. The method of Claim 1 wherein the antineoplastic agent is leucovorin.
 - 18. The method of Claim 1 wherein the antineoplastic agent is levamisole.
- 25 19. The method of Claim 1 wherein the antineoplastic agent is megestrol.
 - 20. The method of Claim 1 wherein the antineoplastic agent is mitoxantrone.
- 21. The method of Claim 1 wherein the 30 antineoplastic agent is paclitaxel.

13

WO 00/38730 PCT/US99/30693

-178-

22. The method of Claim 1 wherein the antineoplastic agent is raloxifene.

- 23. The method of Claim 1 wherein the antineoplastic agent is retinoic acid.
- 5 24. The method of Claim 1 wherein the antineoplastic agent is tamoxifen.
 - 25. The method of Claim 1 wherein the antineoplastic agent is thiotepa.
- 26. The method of Claim 1 wherein the10 antineoplastic agent is topotecan.
 - 27. The method of Claim 1 wherein the antineoplastic agent is toremifene.
 - 28. The method of Claim 1 wherein the antineoplastic agent is vinorelbine.
- 15 29. The method of Claim 1 wherein the antineoplastic agent is vinblastine.
 - 30. The method of Claim 1 wherein the antineoplastic agent is vincristine.
- 31. The method of Claim 1 wherein the20 antineoplastic agent is selenium (selenomethionine).
 - 32. The method of Claim 1 wherein the antineoplastic agent is sulindac sulfone.
 - 33. The method of Claim 1 wherein the antineoplastic agent is effornithine (DFMO).
- 25 34. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

10

1)

4)

$$H_2N$$

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

5 2)
5-chloro-3-(4-(methylsulfonyl)phenyl)-2(methyl-5-pyridinyl)pyridine,

3)
2-(3,5-difluorophenyl)-3-4(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3phenyl-2(5H)-furanone,

5 6)

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

 N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,

8)

10

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

 9)

10)

5 11)

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

12)

10

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

15

13)

CI OC_2H_5 CF_3

14)

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

15)

5

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

į

3-(4-chlorophenyl)-4-[4(methylsulfonyl)phenyl]-2(3H)-oxazolone,

5 17)

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

The light state party party with the term of the party of them party of the party o

19)

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

5 20)

10

3-(4-fluorophenyl)-4-[4(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

4-[5-pheny1)-3-(trifluoromethy1)-1H-pyrazol-1-yl)benzenesulfonamide,

5 23)

$$H_2N$$
 CF_3

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-

pyrazol-1-yl]benzenesulfonamide,

N-[2-(cyclohexyloxy)-4nitrophenyl]methanesulfonamide,

5 26)

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

10

3-(4-chlorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

WO 00/38730

28)

3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5 29)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide,

30)

10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

5 32)

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide,

33)

10

1-fluoro-4-[2-[4(methylsulfonyl)phenyl]cyclopenten-1yl]benzene,

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5 35)

3-[1-[4-(methylsulfonyl)phenyl]-4(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

5 37)

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

$$H_2N$$
 CF_2H

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

5 40)

[1,1':2',1"-terphenyl]-4-sulfonamide,

41)

10

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

The first that that the state of the control of the state of the state

5

0=S 0-NH₂

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

CI NH₂ OCF₃

5 47)
MeS
SO₂NH₂

$$SO_2NH_2$$
 CH_3 , and

H₂NO₂S OEt

35. The method of Claim 1 wherein the

10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4- (methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

- 36. The method of Claim 1 wherein the cycloo7xygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.
- 37. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

38. The method of Claim 1 wherein the 10 cyclooxygenase-2 inhibitor is

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

5

The first condition with the second of the s

39. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

- 40. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide.
- 41. The method of Claim 1 wherein the 10 cyclooxygenase-2 inhibitor is

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

- 42. The method of Claim 1 wherein the neoplasia is selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.
- 43. The method of claim 1 wherein the neoplasia is selected from the group consisting of acral lentiginous 20 melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma,

-196-

basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma,

- 5 cystadenoma, endodermal sinus tumor endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma,
- hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma,
- leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular
- 20 melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoplastoma, rhabdomyosarcoma,
- 25 sarcoma, serous carcinoma, small cell carcinoma, soft
 tissue carcinomas, somatostatin-secreting tumor,
 squamous carcinoma, squamous cell carcinoma,
 submesothelial, superficial spreading melanoma,
 undifferentiated carcinoma, uveal melanoma, verrucous
 30 carcinoma, vipoma, well differentiated carcinoma, and

Wilm's tumor.

-197-

A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to the mammal a therapeutically effective amount of a combination of radiation therapy / a cylooxygenase-2 inhibitor, and one or more antineoplastic agents, wherein said antineoplastic agents are selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, fluoxymestrine, 10 gemcitabine, goserelin, irinqtecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, ráloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, 15 vinblastine, vincristine, selenium (selenomethionine), sulindac sulfone, exemestane and effornithine (DFMO).

is selected from the group consisting of acral lentiginous melanoma, attinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, 20 adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, 25 chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenodarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastiinoma, germ cell tumors, glioblastoma, 30 glucagonoma, hemangiblastomas, hemangioendothelioma,

45. The method of Claim 44 wherein the neoplasia

Wilm's tumor.

hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, 5 leiomyosarcoma, lentigo maligna/melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, /meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular 10 melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypentide, papillary serous adenocarcinoma, pineal cell pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, 15 sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous 20 carcinoma, vipoma, well differentiated carcinoma, and

46. The method of Claim 44 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

4)

$$H_2N$$
 S F O O F

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

5 2)
5-chloro-3-(4-(methylsulfonyl)phenyl)-2(methyl-5-pyridinyl)pyridine,

3)
2-(3,5-difluorophenyl)-3-410 (methylsulfonyl)phenyl)-2-cyclopenten-1-one,

H₂NO₂S CH₃

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3phenyl-2(5H)-furanone,

5 6)

4-(5-methyl-3-phenylisoxazol-4-

yl) benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,

8)

10

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

The first that the task which is then or the first that the task that th

9)

10)

5 11)

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

12)

10

N-(4-nitro-2-phenoxyphenyl) methanesulfonamide,

13)

15)

$$CI$$
 O
 O
 CF_3

14)

CH₃

O=S

H₃C

CH₃

5 3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

NHSO₂CH₃ F

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1oxo-1H-inden-5-yl]methanesulfonamide, HTM HEM HEM THE THE THE HEM THE HIM THE HIM HOW HE HAVE THE HE HAVE THE HE HAVE THE HEM HOW THE HEM HOW THE HEM HOW THE HEM HOW THE HEAD THE HEM HOW THE HEAD THE HEM HOW THE HEAD THE

CI N H₃C

> 3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

5 17)

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

$$H_2N$$
 CH_3

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

5 20)

3-(4-fluorophenyl)-4-[4(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,

5 23)

$$H_2N$$
 CF_3

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

N-[2-(cyclohexyloxy)-4nitrophenyl]methanesulfonamide,

5 26)

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

10

3-(4-chlorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5 29)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide,

30)

10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

5 32)

3-[(2,4-dichlorophenyl)thio]-4[(methylsulfonyl)amino]benzenesulfonamide,

33)

10

1-fluoro-4-[2-[4(methylsulfonyl)phenyl]cyclopenten-1yl]benzene,

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5 35)

3-[1-[4-(methylsulfonyl)phenyl]-4(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

5 37)

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

38)

10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

$$H_2N$$
 CF_2H

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

5 40)

[1,1':2',1"-terphenyl]-4-sulfonamide,

41)

10

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

43)

5

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

10

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

The first principle of the first of the principle of the

CI O Na

CI NH₂ CF₃

MeS SO_2NH_2 CH_3 and

H₂NO₂S OEt

47. The method of Claim 44 wherein the

10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

- 48. The method of Claim 44 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.
- 49. The method of Claim 44 wherein the 5 cyclooxygenase-2 inhibitor is

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

50. The method of Claim 44 wherein the 10 cyclooxygenase-2 inhibitor is

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

51. The method of Claim 44 wherein the

15 cyclooxygenase-2 inhibitor is

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

- 52. The method of Claim 44 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide.
- 53. The method of Claim 44 wherein the cyclooxygenase-2 inhibitor is

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

- 54. The method of Claim 44 wherein the 10 antineoplastic agent is anastrozole.
 - 55. The method of Claim 44 wherein the antineoplastic agent is calcium carbonate.
 - 56. The method of Claim 44 wherein the antineoplastic agent is capecitabine.
- 15 57. The method of Claim 44 wherein the antineoplastic agent is carboplatin.
 - 58. The method of Claim 44 wherein the antineoplastic agent is cisplatin.
- 59. The method of Claim 44 wherein the 20 antineoplastic agent is Cell Pathways CP-461.
 - 60. The method of Claim 44 wherein the antineoplastic agent is cyclophosphamide.
 - 61. The method of Claim 44 wherein the antineoplastic agent is docetaxel.
- 25 62. The method of Claim 44 wherein the antineoplastic agent is doxorubicin.

-216-

- 63. The method of Claim 44 wherein the antineoplastic agent is etoposide.
- 64. The method of Claim 44 wherein the antineoplastic agent is fluorouracil (5-FU).
- 5 65. The method of Claim 44 wherein the antineoplastic agent is fluoxymestrine.
 - 66. The method of Claim 44 wherein the antineoplastic agent is gemcitabine.
- 67. The method of Claim 44 wherein the 10 antineoplastic agent is goserelin.
 - 68. The method of Claim 44 wherein the antineoplastic agent is irinotecan.
 - 69. The method of Claim 44 wherein the antineoplastic agent is ketoconazole.
- 15 70. The method of Claim 44 wherein the antineoplastic agent is letrozol.
 - 71. The method of Claim 44 wherein the antineoplastic agent is leucovorin.
- 72. The method of Claim 44 wherein the 20 antineoplastic agent is levamisole.
 - 73. The method of Claim 44 wherein the antineoplastic agent is megestrol.
 - 74. The method of Claim 44 wherein the antineoplastic agent is mitoxantrone.
- 75. The method of Claim 44 wherein the antineoplastic agent is paclitaxel.
 - 76. The method of Claim 44 wherein the antineoplastic agent is raloxifene.
- 77. The method of Claim 44 wherein the 30 antineoplastic agent is retinoic acid.

30

-217-

- The method of Claim 44 wherein the antineoplastic agent is tamoxifen.
- The method of Claim 44 wherein the antineoplastic agent is thiotepa.
- 5 80. The method of Claim 44 wherein the antineoplastic agent is topotecan.
 - 81. The method of Claim 44 wherein the antineoplastic agent is toremifene.
- The method of Claim 44 wherein the 10 antineoplastic agent is vinorelbine.
 - The method of Claim 44 wherein the antineoplastic agent is vinblastine.
 - The method of Claim 44 wherein the antineoplastic agent is vincristine.
- 15 The method of Claim 44 wherein the antineoplastic agent is selenium (selenomethionine).
 - The method of Claim 44 wherein the antineoplastic agent is ursodeoxycholic acid.
- The method of Claim 44 wherein the 20 antineoplastic agent is sulindac sulfone.
 - The method of Claim 44 wherein the antineoplastic agent is effornithine (DFMO).
 - The method of Claim 44 wherein the neoplasia is selected from the group consisting of lung cancer,
- breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.
 - A combination comprising a cyclooxygenase-2 inhibit $\phi_{L_{\ell}}^{\mu}$ and one or more antineoplastic agents, wherein said antineoplastic agents are selected from the group consisting of anastrozole, calcium carbonate, capecitabine,

carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol,

mitoxantrone, paclitaxel, ralloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), sulindac sulfone, exemestane and effornithine (DFMO).

91. The combination of Claim 90 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)

15

20

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)2-fluorobenzenesulfonamide,

5-chloro-3-(4-(methylsulfonyl)phenyl)-2(methyl-5-pyridinyl)pyridine,

3)

2-(3,5-difluorophenyl)-3-4(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

4)

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

5)

5

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3phenyl-2(5H)-furanone,

6)

10

4-(5-methyl-3-phenylisoxazol-4-

yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-

4yl]phenyl]sulfonyl]propanamide,

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

5 9)

10)

11)

10

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

. 12)

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

13)

$$CI \xrightarrow{O \\ CF_3} CC_2H_5$$

14)

5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

10 15)

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

16)

3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

17)

5

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

$$H_2N_3$$
 CH_3

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

5 20)

3-(4-fluorophenyl)-4-[4(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,

5 23)

$$H_2N$$
 CF_3

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

N-[2-(cyclohexyloxy)-4nitrophenyl]methanesulfonamide,

5 26)

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

27)

10

3-(4-chlorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5 29)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl) amino]benzenesulfonamide,

30)

10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

5 32)

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide,

33)

10

1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1yl]benzene,

34)

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1Hpyrazol-1-yl]benzenesulfonamide,

35)

5

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

36)

10

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1Himidazol-1-yl]benzenesulfonamide,

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

5 38)

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

39)

10

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

[1,1':2',1"-terphenyl]-4-sulfonamide,

41)

5

See Hill help the role that it will not the first the second to the seco

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

42)

4-(2-phenyl-3-pyridinyl) benzenesulfonamide,

10

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

5 44)

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

45)

46)

10

$$\begin{array}{c} \text{MeS} \\ \text{SO}_2\text{NH}_2 \\ \\ \text{CH}_3 \end{array} \text{, and}$$

48)

- 5 92. The combination of Claim 90 wherein the cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.
 - 93. The combination of Claim 90 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.
 - 94. The combination of Claim 90 wherein the cyclooxygenase-2 inhibitor is

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

10

15

5

10

95. The combination of Claim 90 wherein the cyclooxygenase-2 inhibitor is

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone.

96. The combination of Claim 90 wherein the cyclooxygenase-2 inhibitor is

4-(5-methyl-3-phenylisoxazol-4-

yl)benzenesulfonamide.

- 91. The method of Claim 1 wherein the antineoplastic agent is anastrozole.
- 92. The method of Claim 1 wherein the antineoplastic agent is calcium carbonate.
 - 93. The method of claim 1 wherein the antineoplastic agent is exemestane.
 - 94. The method of claim 44 wherein the antineoplastic agent is exemestane.
- 20 95. The method of claim 90 wherein the antineoplastic agent is exemestane.
 - 98. The method of Claim 44 wherein the combination is administered in a sequential manner.

The first pass past part of the the term of the first of the past part of the first of the first

AL

99. The method of Claim 44 wherein the combination is administered in a substantially simultaneous manner.